REMARKS

I. Status of the claims

Claims 1, 4-7, 9-13, 15-16, 18, 20-21, 24-25, and 27-44 are pending in the application. Claims 18, 20-21, 24-25, and 27 have been withdrawn by the Examiner as directed to non-elected subject matter.

By this amendment, Applicants have canceled claims 8 and 23, amended claims 9, 10, 15, 16, 28, 29, 35, 37, and 39 and added new claims 41-44. Exemplary support the for the new claims can be found throughout the specification, for example, at page 5, lines 14-19, page 6, lines 5-24, Figures 1-4, and the Examples. Accordingly, no new matter has been introduced by these amendments.

Applicants also expressly reserve the right to present the subject matter canceled from this application in future prosecution.

II. Rejection under 35 U.S.C. § 102(e) based on U.S. Patent Application Publication No. 2005/0142139

The Examiner rejects claims 1, 4-8, 10-13, 15-16, 23, and 28-40 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Application Publication No. 2005/0142139 to Schulke *et al.* ("the '139 publication"). (Office Action at page 3.) Applicants respectfully disagree with and continue to traverse the rejection. The rejection is also moot with respect to canceled claims 8 and 23.

To establish a *prima facie* case of anticipation, the Examiner must show that one single reference discloses, either expressly or inherently, each and every element of the pending claims. M.P.E.P. § 2131. Applicants submit that the rejection over the '139

publication fails to meet this requirement because the '139 publication is not directed to an "immunoglobulin" preparation.

Instead, the '139 publication is directed to a CD4-IgG2 chimeric heterotetramer - an engineered fusion protein that contains domains from the CD4 protein as well as domains from an IgG2 protein. (*See* the '139 publication, paragraph [0003].) As described in the '139 publication, CD4-IgG2 "is a novel chimeric protein in which polypeptides comprising both the heavy and light chain constant regions of human IgG2 have been fused to the V1 and V2 gp120-binding domains of human CD4." (*Id.*, paragraph [0005].)

Applicants recognize that CD4 contains immunoglobulin-like heavy and light chain domains, and that the CD4-IgG2 fusion protein has an immunoglobulin-like fold. To the extent that any of Applicants' prior remarks could be misinterpreted to mean that the CD4-IgG2 fusion protein disclosed in the '139 publication does not have such a general immunoglobulin-like folded structure, Applicants expressly withdraw reliance on those remarks.

However, the CD4-IgG2 fusion protein of the '139 publication is **not** an "immunoglobulin," as defined in the present application. (*See, e.g.,* page 5, lines 14-24, and Example 2, at pages 9-11.) For instance, that fusion protein is not "an antibody preparation wherein the antibodies may be of any idiotype but preferably IgG, IgA, or IgM." (*See Id.* at page 5, lines 14-24.) It is also not a "polyclonal or monoclonal" molecule, as those terms only refer to antibodies. (*See Id.*) And it is not prone to the sort of idiotype/anti-idiotype dimerization that the instant specification discusses at length. (*See, e.g.*, page 2, lines 24-26, page 10, lines 14-21, and Tables 1 and 2.)

This fusion protein is also not an "immunoglobulin" as that term is commonly defined in the art. For example, the university textbook *Molecular Biology of the Cell*, by B. Alberts et al., 3rd Ed. 1994, defines "immunoglobulin" as "[a]n antibody molecule." (See excerpt attached with the enclosed SB-08 form.) Similarly, the university textbook *Cellular and Molecular Immunology* by A.K. Abbas et al., 4th Ed. 2000, defines "immunoglobulin" as "synonymous with antibody." (See attached SB/08 form and excerpt.) CD4 is not an antibody. Nor is a CD4-IgG2 chimeric fusion protein an antibody. The CD4-IgG2 chimeric fusion protein is also not an "IgG" or an "IgA" or an "IgM" as recited in claims 15 and 29-40. Therefore, because an "immunoglobulin" is an antibody, and CD4 is not an antibody, a CD4-IgG2 fusion protein cannot be considered an "immunoglobulin."

Thus, for all of the reasons above, the '139 publication cannot anticipate any of the currently pending claims. Applicants respectfully request the withdrawal of this rejection.

III. Rejection under 35 U.S.C. § 103(a) based on U.S. Patent Application Publication No. 2005/0142139

The Examiner rejects claims 1, 7-9, 28, and 33-40 under 35 U.S.C. §103(a) as allegedly obvious over the '139 publication. (Office Action at page 5.) Applicants respectfully disagree with and traverse the rejection and note that it is also moot with respect to canceled claim 8.

Several basic factual inquiries must be made to determine whether the claims of a patent application are obvious under 35 U.S.C. § 103. These factual inquiries are set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), and require the Examiner to:

(1) Determine the scope and content of the prior art;

(2) Ascertain the differences between the prior art and the claims in issue;

(3) Resolve the level of ordinary skill in the pertinent art; and

(4) Evaluate evidence of secondary considerations.

The obviousness or non-obviousness of the claimed invention is then evaluated in view of the results of these inquiries. *Graham*, 383 U.S. at 17-18; *see also KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 1734 (2007). The Federal Circuit has stated that "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusions of obviousness." M.P.E.P. § 2142 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)); *see also KSR*, 127 S. Ct. at 1741 (quoting Federal Circuit statement with approval). "To reach a proper determination under 35 U.S.C. § 103, the Examiner must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention 'as a whole' would have been obvious at the time to that person." M.P.E.P. § 2142.

Differences Between the '139 Publication and the Claims

As mentioned above, the '139 publication is directed to a specific fusion protein, a CD4-IgG2 chimeric heterotetramer, which is not an immunoglobulin. But even if, merely for the sake of argument, the '139 publication was applicable to the present invention, the '139 publication teaches away from the instant claims in several respects. For example,

- it teaches a higher pH range than claimed here, and its formulations therefore require a histidine buffer not required here,
- it teaches that glycine and alanine are superior stabilizers compared to other amino acids, and
- it teaches a lower concentration of amino acid stabilizer than used here.

Specifically, the '139 publication teaches that its pharmaceutical formulation has a pH of between about 5.5-6.5 and **not** about 4.2 to about 5.4 as recited in independent claims 1 and 8. Further, the '139 inventors state that they had conducted an experiment to evaluate the effect of pH on the stability of their formulation. (*See* the '139 publication, paragraphs [0073], [0074], and [0126].) In doing so, the '139 publication describes that "[t]o evaluate the effect of pH, samples in base buffer and approximately 25 mM NaCl at pH's ranging from 4 to 8 and a sample in PBS were incubated at 50° C. for 0, 3, or 7 days and analyzed." (*Id.* paragraph [0126].) The '139 publication then reports that:

> All samples showed some degree of suspended precipitate at day 7. On days 3 and 7, samples at pH 7.5 and 8 were cloudy with precipitate. HPLC-SEC analysis showed that **samples in buffers at pH 6 and 6.5 yielded the highest recoveries (~80%) of CD4-IgG2 monomer at day 7 compared to ~25-55% recovery at other pH values.** The RALS data suggested that the optimal pH range for CD4-IgG2 was 5.5-7. Measurement of EF showed that pH 6 overall exhibited the highest emission ratios, indicating less hydrophobicity and less denaturation. Thus, **the optimal pH for maintaining protein stability was determined by apparent hydrophobicity analysis to be pH 6**. However, subjecting samples to shear stress and measuring CD4-IgG2 monomer recovery by HPLC-SEC, recovery of total protein by UV spectroscopy, and **turbidity by RALS, suggested that CD4-IgG2 could best withstand shear stress at pH 6.5**.

(*Id.* (emphasis added).) Thus, the '139 publication specifically teaches that the samples in buffers at pH 6 and 6.5 yielded the highest recoveries as compared to the other pH values. Thus, from the '139 publication, there would be no reason to use a lower pH range, such as about 4.2 to about 5.4.

Second, the '139 publication requires the presence histidine to maintain the stability of its CD4-IgG2 formulation. The present claims, however, do not require histidine. (*See id.,* paragraphs [0008]-[0013].)

Third, while the '139 publication states that its formulation may further comprise an amino acid stabilizer that could be selected from alanine, glycine, proline, and glycylglycine, the '139 publication fails to provide any teaching or suggestion that would have prompted a skilled artisan to specifically choose proline as a stabilizer. To the contrary, the working examples of the '139 publication mostly contain glycine as an amino acid stabilizer and the publication explains that glycine is preferred. (*See id.*, Tables 2-4 and 7-9; paragraphs [0032] and [0039].) Indeed, in evaluating the effect of amino acid stabilizers, the '139 publication states that "[g]lycine and alanine showed slightly higher percentage recoveries than the other histidine-based formulation." (*Id.*, paragraph [0138].)

Fourth, as conceded by the Examiner, the '139 publication merely teaches that its amino acid stabilizing agent is present at a concentration of between about 25-150 mM. A skilled artisan would not consider a maximum concentration of "about 150 mM" to encompass a concentration of 200 mM or higher. Moreover, a skilled artisan would have had no reason nor motivation to increase the concentration of the '139 publication's amino acid stabilizer up to 0.2-0.4 M as recited in several pending claims.

As stated in the Declaration of Reinhard Bolli filed February 9, 2009, "a skilled artisan would have no reason nor motivation to increase the proline concentration beyond 200 mM because it would increase the cost of the preparation and the osmolarity of the solution, both of which could have led to undesirable outcomes for clinical applications." (*Id.*, ¶ 13.) Likewise, if only for the sake of argument, the '139 publication were applicable to the rejected claims, a skilled artisan knowing nothing of the instant application would have had no motivation whatsoever to move in the direction of the present claims.

The '139 Publication Does Not Apply to Claims 29-44

Applicants note that claims 29-44 as amended or newly added herein, recite "a polyclonal IgG" formulation. Because such polyclonal IgG molecules are drawn from the blood or plasma of many donors, they are prone to idiotype/anti-idiotype dimerization, which may cause adverse events in patients. This dimerization problem adds further technical difficulties not addressed in the '139 publication because a CD4-IgG2 fusion protein is a single protein molecule rather than a mixture of proteins with different sequences, and thus is not prone to such dimerization.

Reducing or preventing such idiotype/anti-idiotype dimerization is a major technical issue for a developer of a polyclonal IgG formulation as claimed here, particularly one that is to be liquid and not subject to lyophilization and reconstitution, as also claimed in claims 34, 36, 28, and 40-44. Therefore, the '139 publication does not apply to claims 29-44 for this additional reason.

The '139 Publication Should be Considered in the Context of the Prior Art as a Whole

Furthermore, the '139 publication, even if, for the sake of argument, it were applicable to the rejected claims, should be considered in the context of the teachings of the prior art as a whole at the relevant time. One of ordinary skill, knowing nothing of the instant application, reviewing the '139 publication in the context of prior art documents that concern immunoglobulin formulations, would not have been led toward Applicants' invention.

The prior art as a whole does not lead one of ordinary skill toward the use of proline as a stabilizer for an immunoglobulin or IgG formulation or polyclonal IgG formulation. Other publications teach stabilizing immunoglobulin formulations with a variety of other agents such as polyethylene glycol (PEG), nonionic detergents or surfactants, albumin protein, several different sugars such as glucose, mannose, trehalose, sucrose, and/or several different types of polyols such as mannitol or sorbitol, as well as chemicals such as nicotinamide and nicotinamide derivatives. For example, U.S. Patent No. 6,162,904 teaches IgG compositions including a D-sorbitol stabilizer. (Col. 9, lns. 4-11.) U.S. Patent No. 6,281,336 teaches IgG compositions with maltose or sorbitol stabilizers and also comments that IgG compositions could include ingredients such as sugar alcohols and saccharides such as sorbitol, mannose, glucose, trehalose, and maltose, proteins such as albumin, amino acids such as lysine and glycine, and organic agents such as PEG. (*See* col. 5, lns. 9-22; col. 9, lns. 17-31, col. 12, lns 46-64, and col. 14, lns. 54-58.) U.S. Patent No. 5,593,675 teaches an anti-D IgG formulation that may include albumin, an amino acid such as glycine, a disaccharide such as sucrose, or a saccharide such as mannitol. (Col. 4, lns 43-57.) European

Patent Application No. 0 852 951 (published in English as U.S. Patent Publication No. 2008-0286280) discusses the use of human serum albumin, monosaccharides, disaccharides, and trisaccharides such as glucose, mannose, galactose, fructose, sorbose, sucrose, lactose, maltose, trehalose, raffinose, cellobiose, gentiobiose, and isomaltose, basic amino acids such as arginine, lysine, histidine, and ornithine, acidic amino acids such as glutamic acid and aspartic acid, neutral amino acids such as isoleucine, leucine, and alanine, and aromatic amino acids such as phenylalanine, tryptophan, and tyrosine. It also discusses glucosamine, N-methylglucosamine, galactosamine, and neuraminic acid, as well as PEG, and surfactants such as Tween. (U.S. Patent Publication No. 2008-0286280 at paragraphs [0028]-[0034].)

Hence, the prior art when considered as a whole, including the '139 publication, provides a very large list of possibilities for immunoglobulin or IgG formulation excipients, including molecules from a variety of different chemical classes and molecules with diverse chemical and physical properties, without any clear direction to guide one of ordinary skill toward a specific formulation.

Even as far as the use of amino acids is concerned, publications concerning immunoglobulin or polyclonal IgG formulations that mention amino acids generally do not mention proline at all. (See, e.g., U.S. Patent Nos. 6,281,336 and 5,593,675 and EP Publication No. 0 852 951; U.S. Patent No. 5,831,736.)

Furthermore, several different commercial polyclonal IgG and immunoglobulin formulations were known in the art as of the filing date of this application. Some of those formulations are described, for instance, in U.S. Patent No. 6,281,336, in the table at column 18, and in an article by Buckley et al. (Table 1, page 111). As can be seen

from those documents, the majority of the commercial formulations were subject to lyophilization and the lyophilized formulations were stabilized by:

- maltose, glycine, and albumin (Gammagard)
- sucrose and albumin (Gammar IV)
- sucrose and PEG (Iveegam)
- sucrose (Sandoglobulin)
- D-mannitol, albumin, and PEG (Venoglobulin)
- maltose and albumin (Gammonativ)

Liquid polyclonal IgG formulations that were available were stabilized, for example, by maltose and glucose (Octagam) or maltose alone (Gamimune). Moreover, U.S. Patent No. 6,281,336 suggests using saccharides in a liquid polyclonal IgG preparation as "they have good stabilizing properties and are quickly excreted." (*Id.* at col. 20, lns. 61-67.)

Therefore, standing in the shoes of a person of ordinary skill in this art at the time this application was first filed, and knowing nothing about the present disclosure or claims, there would have been no reason to select proline as stabilizer for an immunoglobulin or IgG formulation. And a person of ordinary skill who wished to try to stabilize a commercial immunoglobulin or IgG formulation with something other than a combination of albumin, PEG, glycine, sucrose, maltose, or mannose would have had a nearly infinite list of possibilities to try, including chemicals from a myriad of different classes. There is also no reason for one of ordinary skill in the art to have supposed that proline in the absence of nicotinamide or a formulation comprising a stabilizer consisting essentially of proline, could be sufficient to provide adequate stability.

Thus, given that the '039 publication teaches away from several aspects of the instant claims and also does not pertain to immunoglobulins or IgG formulations, coupled with the myriad possibilities for attempting to formulate immunoglobulins disclosed in the art, one of ordinary skill would not have been motivated to choose to formulate immunoglobulins according to the specific parameters claimed here.

Thus, the above reasons, the Examiner has failed to establish a *prima facie* case of obviousness in view of the '139 publication.

The Claimed Invention Shows Unexpected Results

Finally, even if, for the sake of argument one assumes that a *prima facie* case of obviousness has been established, the instant polyclonal IgG preparations show an unexpectedly high stability and a low level of toxic side effects. The attached *Vox Sanguinis* article by M. Cramer et al. describes Applicants' commercial product Privigen®, which is a liquid polyclonal IgG preparation comprising about 10% polyclonal IgG formulated with 250 mM L-Proline at pH 4.8, and which is not subject to lyophilization before use. (*See* Abstract and Discussion, first paragraph.) The article further points out that "liguid IVIG formulations have limited shelf-lives. Long-term storage of liquid IVIG formulations has therefore required the use of refrigerated conditions until now." (Page 1, column 1; Discussion, first paragraph.) For instance, the article notes that IVIG formulations at a lower IgG concentration of 5% "may be stored at room temperature for a period of up to 1 year" and that "[t]he optimal storage temperature for currently available 10% IVIG solutions is 5 °C, for a maximal storage time of 36 months [3 years]. **These solutions are stable at room temperature for**

only a few months." (Discussion section, first column, page 6, emphasis added.) In contrast, Privigen®, despite being at 10% IVIG preparation, is stable for 3 years in storage at room temperature. (*See* Abstract.) That is three times longer than the maximum storage time for a 5% IgG formulation of the prior art noted above.

Applicants submit that one of ordinary skill in the art would not have expected that such a high degree of stability could have been achieved through the use of a proline stabilizer in the absence of nicotinamide.

For all of the reasons above, Applicants respectfully request the Examiner to withdraw this rejection.

IV. Rejection under 35 U.S.C. § 102(b) based on U.S. Patent No. 5,831,736

The Examiner rejects claims 8, 10-11, 15-16, and 28-40 over U.S. Patent No. 5,831,736 (the '736 patent). (Office Action at 6-7.) This rejection is moot with regard to claim 8 and claims 10-11, 15-16, and 28-40 to the extent they depend on canceled claim 8. Furthermore, claims 10-11, 15-16, and 28-40 all currently depend from claim 1, which recites that "the preparation does not comprise nicotinamide." In contrast, the '736 patent teaches compositions comprising nicotinamide. Thus, the '736 patent cannot anticipate any of those claims.

Applicants respectfully request the withdrawal of this rejection.

V. Rejection under 35 U.S.C. § 103(a) based on U.S. Patent No. 5,831,736

The Examiner also rejects claims 9-10 and 12-13 as allegedly obvious over the '736 patent. (Office Action at 7-8.) This rejection is moot because amended claims 9-10 and 12-13 depend from claim 1, which recites that "the preparation does not comprise nicotinamide." In contrast, the '736 patent teaches nicotinamide-comprising

compositions. Thus, the '736 patent does not render any of those claims obvious and Applicants respectfully request the withdrawal of the rejection.

VI. Conclusion

In view of the foregoing remarks, Applicants submit that the claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration of this application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 16, 2010

By: _____
Elizabeth A. Doherty
Reg. No. 50,894